REMARKS

I. Introduction

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claims 24-28 are new.

Claim 24 is supported by the description on page 18, lines 15 to 21 of the English specification, "As can be seen from the description in WO)(/14580, the hybridoma- FERM BP-5233"; and pages 6-7, "The hybridoma produced by the antibody for use in the present invention can be basically, - or a peptide or a polypeptide containing an epitope recognized by anti-HM1.24 antibody."

Claim 25 and 28 are supported by the description on page 14, line 15 to page 15, line 31, "In accordance with the present invention, artificially altered recombinant antibody such as chimeric antibody---851-858."

Claim 26 is supported by the descriptions on page 18, lines 15 to 21, "As can be seen from the description in WO98/14580, the hybridoma ----FERM BP-5233"; as well as page 12, lines 15 to 34, page 14, lines 15 to 21, and page 16, lines 6 to 19.

Claim 27 is supported by the description on page 16, lines 6 to 19, "For chimeric antibody or humanized antibody, the C region of human antibody is used, and as the C region ---the C region of antibody derived from human antibody."

Upon entry of this Amendment, claims 1-7, 15-19 and 21-28 will remain pending in the application.

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

II. Claim Rejection- 35 U.S.C. §102

Claims 15-19, 21 and 22 are rejected by the Examiner under 35 U.S.C. §102 as being anticipated by Morin (US PG PUB 2003/0211498, PCT filed April 4, 2001). Applicants have enabled the use of specific anti-HM1.24 antibodies to treat a disease, while Morin has not. Additionally, Morin has not disclosed the relationship between expression of BST-2 antigen

protein and the disease state. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection.

A. Morin Does Not Enable the Use of Anti-BST-2 Antibody to Treat Ovarian Cancer

Neither the accidental, unappreciated occurrence of a product or process in the prior art, nor the speculative listing of a product (such as a chemical compound) as part of a large number of possible occurrences is an anticipation. *In re Wiggins*, 488 F.2d 538, 179 U.S.P.Q,. 421 (CCPA 1973). The court in *Wiggins*, held that the rejection of appellants' claims under 35 U.S.C. §102(b), based upon a previously published article, was improper since the article itself did not disclose all that was necessary to put the compounds in the hands of the public. The court continued that the compounds listed in the article constituted nothing more than speculation, and therefore did not mandate a rejection of appellants' claims.

The specification and drawings must provide sufficient information about the invention so as "to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same." 35 U.S.C. §112. A specification disclosure is not enabling if unreasonable experimentation is required. *In re Gardner*, 427 F.2d 786, 166 USPQ 138 (CCPA 1970). In the instant case, the one line reference in Morin is speculation regarding a possible future use and does not enable one of ordinary skill in the art to practice the invention.

The Morin reference refers to treatment of ovarian cancer by an anti-BST-2 antibody. However, this reference is speculative and is part of a long list (at least 39) of other tumor cell markers. The Morin reference does not provide experimental proof that ovarian cancer can be treated by an anti-BST-2 antibody. Thus, the Morin reference is simply a speculative listing of a product as part of a large number of possible occurrences, and cannot be the basis for an anticipation. See *Wiggins*.

1. Morin Does Not Disclose Specific Anti-HM1.24 Antibodies

In the Morin reference, **no antibodies were in fact prepared**. Therefore the concrete use of anti-BST-2 antibody would not be clear to a person with ordinary skill in the art. Specifically, Morin does not disclose the use of anti-HM1.24 antibodies. Morin simply lists a

large number of possible occurrences, which cannot support an anticipation rejection. See *Wiggins* . Morin does not give a concrete example or specific examples to use or carry out the claimed invention. Thus, the Morin reference simply constitutes mere speculation.

B. Morin Does Not Address the Discrepancy Between mRNA Levels and Protein Levels

In addition, there is a discrepancy between mRNA levels and protein expression levels. The Morin reference only shows that mRNA levels are increased in ovarian tumor cells, and does not show that protein levels are increased. As shown below, this is not a trivial distinction.

A protein is produced by transcription of a gene encoding the protein to mRNA, and translation of the mRNA to the protein. In this case, there is a post-transcription regulation after the transcription and before the translation. Therefore, a large amount of transcribed mRNA does not necessarily result in a large amount of translated protein. The discrepancy between mRNA levels and protein levels is well known in the art, as can be seen from the following Appendices 1 and 2.

Appendix 1 1, K.M. Ropponen et al., *J. Clin. Pathol.*(2001), 54: 533-538, especially in Abstract, states "Together with reduced AP-2γ expression in high grade carcinomas, this might contribute to tumor progression. The discrepancy between mRNA and protein expression suggests that posttranscriptional regulatory mechanism might modify the availability of functional AP-2γ protein in colorectal carcinoma."

Appendix 2, Fujimoto *et al.*, *Jpn. J. Electroph.* (1996), 40:313 25-29, especially in Abstract, states "A discrepancy between results of nm 23-H1 protein level by Western blot and mRNA level by Northern blot was observed in HCCs," and that "These data suggest that the expression of nm 23-H1 was mainly regulated at a post-transcriptional level." Taken together these references show that protein levels are not always correlated with mRNA levels in tumors.

The Morin reference describes that BST-2 antigen is transcribed into mRNA in large amount in ovarian tumor (Table 4), and that an antibody against a polypeptide encoded by an

ovarian tumor marker gene can be used for treatment of ovarian tumor (Morin, paragraph [0016]).

However, the Morin reference, in Examples, confirms only that an amount of mRNA for a plurality of genes expressed was increased in ovarian tumor cells. Due to the discrepancy between mRNA level and protein level, it is not clear, and not described that a large amount of BST-2 protein is translated.

III. Conclusion

The Morin reference is not enabling, and thus cannot be used as an anticipation reference.

Additionally, the present inventors found, for the first time, that BST-2 (HM1.24) antigen is expressed at the protein level in solid cancers including ovarian cancer. In addition, the present inventors found, for the first time, that an anti-HM1.24 antibody has ADCC activity to solid cancers, and completed the invention for treatment of solid cancers using an anti-HM1.24 antibody.

In conclusion, (1) although the Morin reference describes that a plurality of genes (at the mRNA level) such as BST-2 are expressed in ovarian tumor and therefore can be used as a marker for ovarian tumor, (2) expression of the BST-2 antigen protein is not clear in the Morin reference, and (3) no antibody was prepared in the Morin reference. Thus, concrete therapeutic use of BST-2 is not clear. Furthermore, the Morin reference does not disclose the present invention for treatment of ovarian tumor using anti-BST-2 (HM1.24) antibody.

CONCLUSION

The present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant(s) hereby petition(s) for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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By _____

FOLEY & LARDNER LLP
Customer Number:
22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399

Stephen B. Maebius
Attorney for Applicant
Registration No. 35,264

Benjamin A. Berkowitz
Attorney for Applicant
Registration No. 59,349